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Inflammation and NF- κ B in Alzheimer's Disease and Diabetes

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Abstract. Inflammatory processes are a hallmark of many chronic diseases including Alzheimer's disease and diabetes mellitus. Fairly recent statistical evidence indicating that type 2 diabetes increases the risk of developing Alzheimer's disease has led to investigations of the potential common processes that could explain this relation. Here, we review the literature on how inflammation and the inducible nuclear factor NF- κ B might be involved in both diabetes mellitus and Alzheimer's disease and whether these factors can link both diseases.

Keywords: Alzheimer's disease, inflammation, insulin, insulin-degrading enzyme, nuclear factor- κ B, receptor for advanced glycation endproducts (RAGE), tumor necrosis factor, type 2 diabetes mellitus

INTRODUCTION

Since the beginning of the 20th century, there has been a continuous knowledge-based improvement in healthcare in most industrialized societies. As a result, people in these affluent societies live longer, which has led to an increase in prevalence of age-related neurodegenerative diseases such as stroke and dementia. Diabetes mellitus (DM) has long been known as a risk factor for all vascular diseases, including vascular dementia. Indeed, the epidemiological relationship was recently explored in several large-scale studies. Furthermore, population-based cohort studies, such as the Rotterdam study, have shown that patients with type 2 DM (T2DM) are approximately twice as likely to develop Alzheimer's disease (AD), independent of vascular factors [1,2]. The fact that neurodegenerative diseases are often associated with metabolic diseases such as DM suggests an underlying or aggravating metabolic basis.

Here, we will provide a survey of the multiple levels of interactions between metabolic diseases and AD, and vice versa, and the particular role of inflammatory processes in these interactions. Although inflammation can be considered at least initially as a reaction of tissue against various stressors, chronic inflammation can be seen as part of the pathological process. A number of studies have shown that inflammatory signaling in peripheral organs can influence central nervous system (CNS) functions, while reversely the CNS can have profound effects on peripheral functions. To partially illustrate these multiple mechanisms of interaction, we focus in this review on the transcription factor family NF- κ B, which plays a major role in the initiation of the innate and adaptive immune response. This review concentrates on the role of inflammation and NF- κ B in DM and AD.

INFLAMMATION AND DIABETES MELLITUS

Involvement of inflammation in DM was first recognized more than a century ago, when Ebstein observed that the anti-inflammatory drug sodium salicylate dramatically reduced glucosuria in DM patients [3].

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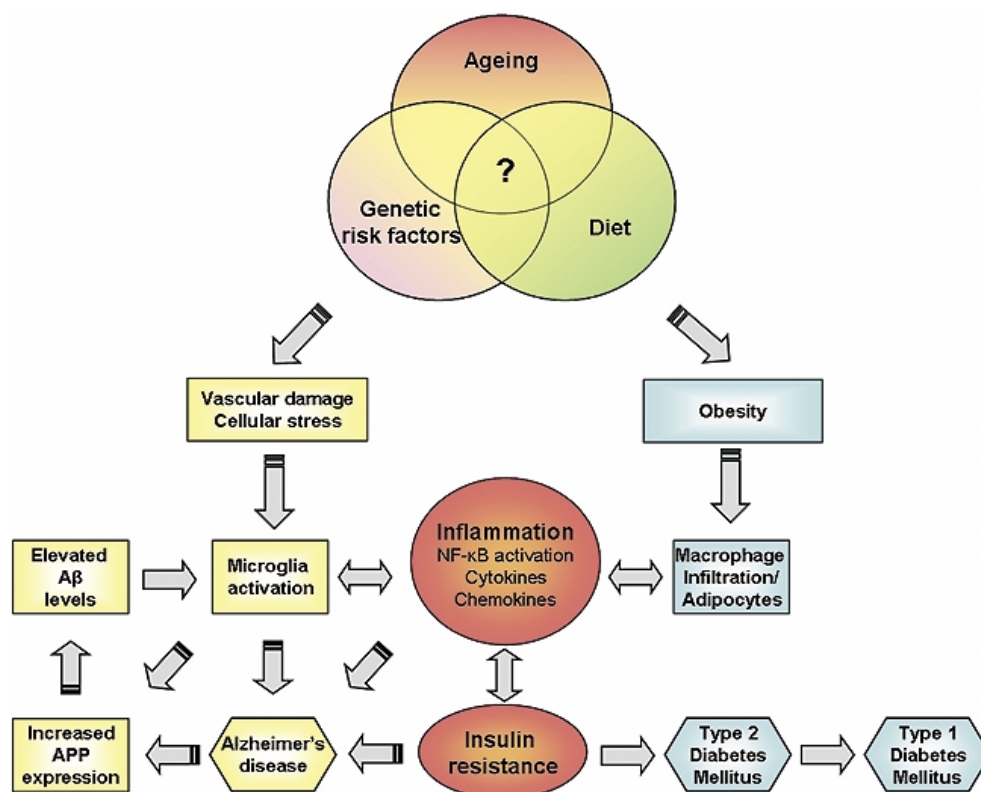


Fig. 1. Inflammation as a central event in the pathogenesis of AD and DM. Aging, diet, genetic risk or other unknown factors can directly or indirectly lead to the pathological changes underlying both diseases. However, chronic inflammation may amplify the pathogenic processes through sustained NF- κ B activation and elevated cytokine levels, which eventually lead to insulin resistance and DM, or result in increased amyloid- β (A β) production and microglia activation, which are symptomatic of AD.

Following the classification of type-1 (i.e., insulin-dependent) and type-2 (i.e., non-insulin-dependent) DM, other, more distinctive inflammatory processes were thought to play a role, especially in the etiology of T2DM. T2DM, which is characterized by an insufficient release of insulin from pancreatic beta-cells to overcome insulin resistance in target tissues, is usually associated with increased levels of markers and mediators of inflammation and acute-phase reactants such as fibrinogen, C-reactive protein (CRP), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), sialic acid, and white cell count. An additional connection between inflammation, obesity, and T2DM in which obese patients exhibited an elevated level of cytokines that caused hepatic insulin resistance has been found (Fig. 1) [4]. The fact that T2DM is a comorbidity of increased visceral adiposity has stimulated interest in the role of adipose tissue as a mediator of inflammatory processes underlying the development of T2DM. Indeed, the proinflammatory cytokine tumor necrosis factor- α (TNF- α), which is produced and secret-

ed by adipose tissue, is found to induce insulin resistance through local and potentially systemic effects on metabolism [5,6]. Subsequent to the idea that fat tissue is a site for the production of cytokines and other bioactive substances, the concept quickly developed beyond TNF- α to include leptin, IL-6, resistin, monocyte chemoattractant protein-1 (MCP-1), angiotensinogen, retinol-binding protein-4, serum amyloid A (SAA), and others [7–9]. Furthermore, TNF- α , IL-6, MCP-1, visfatin, and PAI-1 are highly expressed in activated macrophages and/or other peripheral tissue, as well as in the brain. At this moment, it is not known if cytokines are produced by the adipocytes themselves or by monocytes which have invaded adipose tissue [10]. This knowledge gap has engendered an intense debate.

INFLAMMATION IN ALZHEIMER'S DISEASE

The idea that neuroinflammatory factors play a role in the etiology of AD dates back to 1910, when Fischer

reported that the extracellular deposition of a “foreign” substance in the cerebral cortex induced both a local inflammatory response and the formation of cerebral plaques [11]. Due to the inadequate detection methods at the time, it was not possible to identify the precise structure of this “foreign” substance or to establish the ultimate proof for the involvement of inflammatory molecules. Today, however, it is well known that the major component of the “foreign” substances is the amyloid- β protein (A β). The A β peptide is the result of a proteolytic cleavage of the amyloid- β protein precursor (A β PP). This precursor protein can be processed in two different ways: via amyloidogenic- or via non-amyloidogenic-processing. Non-amyloidogenic processing involves cleavage within the A β sequence by α -secretase, which prevents the formation of A β . On the other hand, the amyloidogenic pathway is mediated by sequential cleavage of A β PP by β -secretase (BACE) and γ -secretase, which results in the generation of A β_{1-40} and A β_{1-42} species [12,13].

This A β peptide plays a central role in the neuroinflammation hypothesis of AD, which states that A β accumulation results in increased levels of inflammatory molecules (e.g., cytokines, chemokines, complement proteins) produced by chronically activated glia. This leads to neuronal damage, which in turn induces further glial activation, and results in a detrimental cycle of neuroinflammation and neurodegeneration [14].

TNF- α is one of the most prominent pro-inflammatory cytokines significantly increased in AD and it plays a central role in initiating and regulating the cytokine cascade during inflammatory responses [15,16]. For example, TNF- α increases the expression of adhesion molecules on the vascular endothelium, which allows leukocytes and immune cells to infiltrate areas of tissue damage and infection [17]. TNF- α exerts its biological functions via two distinct receptors: TNF receptor 1 (TNF-R1) and TNF receptor 2 (TNF-R2). The 55 kDa TNF-R1 (p55/60) is a membrane-receptor and is expressed in most tissues where it can be stimulated by both the membrane-bound and the soluble form of TNF- α . The functions of TNF-R1 range from inducing apoptosis and differentiation to NF- κ B-mediated cell survival [18]. Similar to TNF-R1, also the 75 kDa TNF-R2 (p75/80) is a membrane-receptor, but because of its low affinity to soluble TNF- α , it can be fully activated only by membrane-bound TNF- α . The functions of TNF-R2 are as complex as those of TNF-R1 and are still not revealed in all its detail. It is known that the action of the TNF receptors is strongly dependent on the cell type. For instance, TNF-R2 is able to amplify

apoptotic signals from TNF-R1 in cancer cell lines [19] but has also been reported to mediate neuroprotection, as shown in a model for glutamate-induced excitotoxicity [20]. TNF-R2 exerts its protective properties when pre-stimulated with TNF- α , which suggests a neuroprotective role in the CNS [20,21]. In AD patients, TNF-R1 levels are increased [15], whereas TNF-R2 levels are decreased [22].

Recently, it was demonstrated that overexpression of TNF-R1 promotes A β -induced neuronal death in an A β PP overexpressing mouse model for AD [23]. In contrast, mice lacking TNF-R1 have a decreased amyloid plaque burden, lower expression of BACE, and improved learning abilities compared to controls [24]. Interestingly, the stimulation of both TNF receptors can lead to the activation of NF- κ B, which has binding sites in the promoter regions of both the A β PP and the BACE gene [25]. Mutations in the NF- κ B promoter region of BACE lead to a significant decrease in promoter activity of TNF- α activated glia cells or A β exposed neurons, which indicates an activating role of NF- κ B in BACE expression [26]. In this way, NF- κ B activation can lead to increased A β PP expression and enhanced amyloidogenic A β PP processing. Elevated A β PP and BACE expression will ultimately lead to increased A β production, which can in turn activate glia cells and enhance neuroinflammatory processes.

INFLAMMATION AND THE NF- κ B FAMILY

Inflammation is defined as the local response to tissue injury [27], and NF- κ B is considered as a primary regulator of inflammatory processes. The NF- κ B family of transcription factors is an evolutionarily conserved signaling system that plays an important role in many biological processes in addition to inflammation. NF- κ B was first described in B cells, but it was later shown to exist in an inactive cytosolic form in all cell types, including the nervous system [28]. NF- κ B also plays a central role in the initiation and amplification of inflammation by responding to proinflammatory stimuli such as TNF- α or interleukin-1 (IL-1) [29–31]. As illustrated in Fig. 1, aberrant regulation of NF- κ B leads to the development of many pathological states especially those involving acute inflammation such as AD and DM [32,33].

However, NF- κ B is not the only transcription factor activated under inflammatory conditions. Activation of other transcription factors such as PPAR γ and STAT-1 have also been implicated in AD [34,35].

INVOLVEMENT OF NF- κ B IN DIABETES MELLITUS AND ALZHEIMER'S DISEASE

The NF- κ B family

Different members of the NF- κ B family have been identified in mammalian cells: p65 (RelA), RelB, c-Rel, p50/p105 (NF- κ B1), and p52/p100 (NF- κ B2). NF- κ B1 and NF- κ B2 are synthesized as large precursors, p105 and p100, which are post-translationally processed to the DNA-binding subunits p50 and p52, respectively. All members of the NF- κ B family have an N-terminal 300 amino acid Rel homology domain that allows DNA binding, dimerization, and nuclear localization in common [36]. NF- κ B proteins are present in unstimulated cells as homo- or heterodimers bound to the inhibitor of the kappa B (I κ B) family of proteins I κ B α , I κ B β , I κ B γ , I κ B δ , I κ BNS, Bcl-3, and the p100 and p105 precursor proteins. Association with I κ B prevents the nuclear translocation of the NF- κ B:I κ B complex.

Currently, two NF- κ B activation pathways have been identified (Fig. 2). Classical/canonical NF- κ B activity is stimulated by proinflammatory cytokines, such as TNF- α and IL-1, as well as by pathogen-associated molecular patterns (PAMPs). The binding of these ligands to their respective receptors, i.e., the TNF-R, Toll-like receptor (TLR) and the interleukin-1 receptor (IL-1R) superfamilies, causes activation of various cellular signaling pathways such as the protein kinase C (PKC), mitogen-activated protein (MAP) kinase kinase kinase-1 (MEKK1), and also the PKB/Akt signaling pathway, all of which have the potential to phosphorylate the I κ B kinase (IKK) complex. IKK consists of two catalytic subunits (IKK α and IKK β) and a regulatory subunit (IKK γ). In the canonical pathway, the activated IKK complex predominantly acts through IKK β in an IKK γ -dependent manner to catalyze the phosphorylation of I κ Bs. Upon phosphorylation, I κ B releases NF- κ B, allowing it to translocate to the nucleus and to initiate gene transcription (Fig. 2a). The most commonly released NF- κ B dimer in this pathway is the p50-RelA dimer [37].

The alternative/non-canonical activation pathway is activated by certain members of the TNF cytokine family but not by TNF- α itself and is strictly dependent on IKK α [38]. The target for IKK α homodimers in this pathway is NF- κ B2/p100 (Fig. 2b).

Recent results strongly suggest that the canonical and non-canonical pathways to NF- κ B activation have distinct regulatory functions. Whereas the classical

pathway was found to be mostly involved in innate immunity and maintaining survival of immune cells, the alternative pathway is an important player in adaptive immunity and the development and organization of secondary lymphoid organs and B-cell maturation [39].

NF- κ B regulates several promoters containing variations in a highly divergent consensus DNA-binding sequence. Variations in the DNA-binding site appear to confer regulatory specificity for NF- κ B family members by two general mechanisms. The sequence of the site can determine which coactivators form productive interactions with the bound NF- κ B dimer [40]. This mode of specificity occurs independently of any inherent difference in DNA binding by distinct dimers. A second mechanism conferring specificity of transcriptional regulation involves differential affinity of NF- κ B dimer combinations for different DNA-binding sequences sites. NF- κ B signaling can be switched off through multiple mechanisms, including the new synthesis of I κ B α protein.

The activation and nuclear translocation of classical NF- κ B dimers (mostly p50-RelA) is associated with increased transcription of genes encoding chemokines, cytokines, and adhesion molecules [intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial-leukocyte adhesion molecule 1 (ELAM)], all of which are factors that produce secondary inflammatory mediators [41]. NF- κ B regulates proliferation and apoptosis by controlling the expression of the cellular inhibitors of apoptosis (cIAP1, cIAP2, and XIAP) [42,43], the TNF receptor associated factors (TRAF1 and TRAF2) [43], the bcl-2 homologue A1/Bfl-1, and IEX-IL [44]. Interestingly, NF- κ B activation can thus lead to the expression of the same cytokines that can also regulate its activity, such as IL-1 β and TNF- α . This results in a positive auto-regulatory loop contributing to the amplification of the inflammatory response and the persistence of chronic inflammation at local sites.

NF- κ B and diabetes

After Ebstein's discovery [3] and a somewhat later investigation by Williamson [45], the role of salicylates in the treatment DM were long forgotten, in part because of the fact that the well-established effects of low doses of salicylates to block cyclo-oxygenase enzyme activation of prostaglandin synthesis [46] were far below the concentration of salicylates necessary to induce effects on glucose homeostasis [47]. High doses of salicylates, however, had been found to inhibit

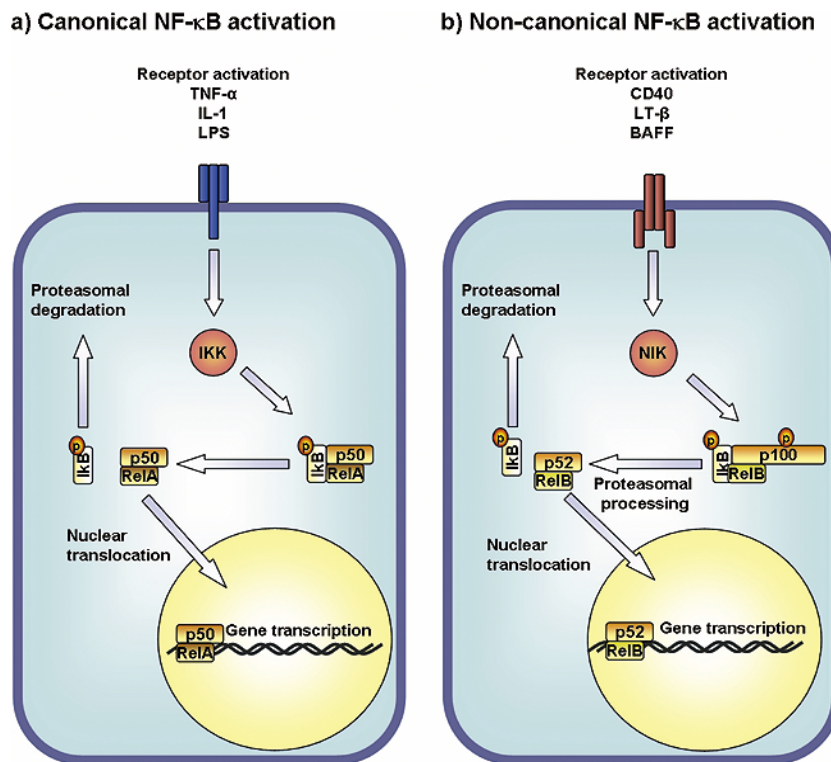


Fig. 2. The activation of NF- κ B transcription factors occurs through two main pathways: a) the canonical and b) the non-canonical NF- κ B activation pathway. During canonical signaling upstream mediators activate the I κ B kinase (IKK) complex to phosphorylate inhibitory I κ B proteins, leading to their ubiquitination and degradation. NF- κ B dimers are then free to bind to DNA and to activate gene transcription. Alternative, non-canonical NF- κ B signaling is mediated by NF- κ B Inducing Kinase (NIK), which induces the partial proteolytic degradation of p100 to p52. RelB, together with p52, translocates to the nucleus and transactivates their target genes.

NF- κ B [47], and its upstream component, I κ B kinase- β (IKK- β). Cai and colleagues [48] were able to induce a T2DM phenotype in mice by selectively expressing IKK β in hepatocytes, characterized by hyperglycemia and insulin resistance. A definitive role for the IKK β /NF- κ B in glucose homeostasis was substantiated when targeted deletion of IKK β in obese and diabetic mice completely reversed insulin resistance in these animals [49–51].

Evidence in support of a critical role of NF- κ B in the pathogenesis in early stages of DM can be described as threefold (regarded as activators, effectors, and as modulators of the NF- κ B activity).

First, in DM, the increase in NF- κ B activators promotes vascular complications. Thus far, at least four molecular mechanisms have been implicated in glucose-mediated vascular diseases. These mechanisms include: glucose-mediated activation of PKC isoforms; increased formation of glucose-derived advanced glycation endproducts (AGEs); the aldose-reductase (AR) pathway; and increased formation of reactive oxygen species (ROS). Furthermore, all of these

pathways have been demonstrated to increase NF- κ B activity. Hyperglycemia leads to the activation of different isoforms of PKC in accordance with tissue types, thus determining the specific kind of DM-induced organ damage [52]. Activation of the AR pathway is necessary for high-glucose-induced TNF- α synthesis and release. In DM, high-glucose mediated TNF- α release has been shown to cause cardiovascular complications [53]. Although targeting PKC isoforms and AR products has proven to be a difficult and challenging task, targeting glucose-derived AGE- receptor for advanced glycation endproducts (RAGE) products became more feasible with the availability of RAGE knockout mice and a competitive decoy for AGEs, soluble RAGE (sRAGE). Diabetic RAGE overexpressing transgenic mice showed exacerbated neuropathy, while inhibition of AGE formation prevented these vascular cell derangements [54,55]. On the other hand, it was found that RAGE knockout mice were resistant to DM-induced neuropathy. In human DM patients, NF- κ B activation is a time consuming process and is associated with increased transcription of the p65 subunit of

NF- κ B [56]. These findings were paralleled by *in vitro* studies, in which it was shown that RAGE-expressing cells induced sustained translocation of p50/p65 subunits of NF- κ B from the cytoplasm into the nucleus. RAGE ligands induce NF- κ B activation by initial degradation of I κ B proteins, followed by new synthesis of the p65 subunit of NF- κ B, although I κ B α and I κ B β are also generated. These findings indicate an important function of *de novo* synthesized p65 subunit in prevailing the NF- κ B auto-inhibitory effects, thus inducing a sustained NF- κ B activation in hyperglycemic conditions [56]. Several reports have shown that IKK β , which is responsible for the activation of NF- κ B, was also increased in insulin-resistant cells [49,51].

The importance of IKK β in insulin resistance was provided by data accumulated from IKK β (+/-) heterozygous mice. Whereas IKK β (-/-) homozygous mice died in embryonic stages due to massive apoptosis in the liver, IKK β (+/-) heterozygous mice were reported to exhibit a stronger insulin sensitivity compared with their wild type littermates [49].

Second, inhibition of NF- κ B effectors, such as iNOS or ICAM proteins mediates beneficial effects reducing DM-induced degeneration of retinal capillaries [57]. In retinas of mice exhibiting streptozotocin-induced DM, the concentrations of NO, of iNOS, the nitration of proteins and leukostasis were significantly increased when compared with non-diabetic mice [58]. Interestingly, in diabetic iNOS-/- mice not all of the above-mentioned abnormalities were detected. In addition, retinas from streptozotocin-induced DM mice were significantly thinner than from non-diabetic control mice, whereas no retinal defects were observed in diabetic iNOS-/- mice. Administration of the iNOS specific inhibitor, N(G)-nitro-L-arginine methyl ester, reduced DM-mediated leukostasis within retinal vessels and blood-retinal barrier permeability [59]. These studies showed that iNOS enzymes play a crucial role in the pathogenesis of vascular lesions detected in early stages of diabetic retinopathy [58,59].

Third, compounds known to inhibit the NF- κ B pathway also inhibit the development of the DM retinopathy or neuropathy. In addition to the augmented oxidative stress-mediated cellular damage, T2DM patients usually present defects of cellular antioxidant defense mechanisms, such as the glutathione redox system, vitamin C-vitamin E cycle, and the α -lipoic acid (LA)/dihydrolipoic acid (DHLLA) redox pair [60]. Antioxidants inhibit the activation of NF- κ B and the development of inflammatory responses in several tissues, including retinas of diabetic animals [61]. Consistent

with these findings, treatment with antioxidants significantly suppressed the NF- κ B activity and reduced plasma markers for lipid oxidation [62]. LA treatment of diabetic neuropathy restored the LA pool, increased the insulin sensitivity [63], raised intracellular glutathione levels [64], prevented glycation of serum albumin [65] and reduced the oxidative stress-mediated NF- κ B activation [62].

NF- κ B in Alzheimer's disease

NF- κ B activation as a central event of inflammation is a common feature of many neurodegenerative diseases such as Huntington, Parkinson, stroke, and particularly of AD. In the brain of AD patients, activated NF- κ B was found predominantly in neurons and glial cells in A β plaque surrounding areas [32,66–68]. The reactive astrocytes in close proximity to the A β plaques produce inflammatory cytokines, including IL-1 β and TNF- α , and iNOS, which generates free radicals such as NO, that can be neurotoxic [69,70]. Several studies have shown that A β and/or a secreted form of A β PP induce an upregulation of NF- κ B activity. Some non-steroidal anti-inflammatory drugs (NSAIDs) have a direct effect on NF- κ B activity, which eventually results in decreased A β PP processing. Flurbiprofen and indomethacin, which target NF- κ B, have been shown to effectively reduce the amyloid load *in vitro* and also in A β PP transgenic mice [71,72]. The activation of NF- κ B leads to the expression of a large variety of pro-inflammatory molecules such as cytokines and chemokines, which could be in part responsible for the neurotoxicity seen in AD. However, there are also reports that certain cytokines, e.g., TNF- α , may trigger NF- κ B activation, which seems to be neuroprotective against A β toxicity in cultured neurons [73,74].

Both pathological hallmarks of AD (A β and hyperphosphorylated tau) are capable of inducing NF- κ B activation via various mechanisms. One common mechanism is the activation of the AGE/RAGE signaling pathway. A β and tau can undergo a non-enzymatic glycation and form AGEs. These AGEs bind to so-called RAGEs and can trigger NF- κ B dependent gene transcription. Furthermore, glycation of A β enhances its aggregation *in vitro* [75], and glycated tau, in addition to hyperphosphorylation, appears to enhance the formation of paired helical filaments (PHFs) [76,77]. In addition, AGEs have been reported to generate reactive oxygen intermediates, leading to the activation of cytokines including IL-1 β and TNF- α , which in turn induce the translocation of NF- κ B to the nucleus [78].

The recently discovered prolyl isomerase protein Pin1, which accelerates the *trans* to *cis* or *cis* to *trans* isomerization of target proteins, is apparently a 'key player' in the pathogenesis of AD [79,80]. Pin1 has been shown to bind to both A β PP and phosphorylated tau, where it stabilizes the non-pathogenic conformations of both proteins. In AD, Pin1 levels are compromised, leading to increased A β formation and reduced tau de-phosphorylation. In addition, Pin1 might have a role in neuronal apoptosis of AD-affected cells as well, either indirectly, via depletion in the levels or aberrant function of Pin1 (resulting from oxidation, phosphorylation or mutations) or directly, via association with specific signaling proteins such as NF- κ B.

During TNF- α treatment, Pin1 binds to the phosphorylated p65/Rel subunit on Thr 254 [81], enhancing NF- κ B DNA binding and transactivation activity. Pin1 binding to p65/Rel inhibits p65 binding to I κ B α , which prevents p65/Rel nuclear export and its subsequent ubiquitin mediated degradation. This leads to enhanced nuclear accumulation, protein stability, and transcriptional activity of NF- κ B towards its target genes, which in turn promotes neuronal survival [81].

Furthermore, a single mutation in p65/Rel abolishes Pin1 binding and destabilizes the protein in HeLa and 293 cells. The source of destabilization has been found to be enhanced ubiquitin mediated proteasomal degradation [81]. Ryo and colleagues [81] suggest that Pin1 stabilizes p65 and prevents its proteasomal degradation, probably by isomerizing the Thr254-Pro motif towards a more stable conformation, possibly indicating that in neurons in which NF- κ B is induced, Pin1 might mediate neuronal survival by stabilizing NF- κ B, resulting in the transcription of its pro-survival target genes. In addition, Pin1 has also been shown to bind to these anti-apoptotic NF- κ B target genes, possibly stimulating survival downstream of NF- κ B signaling as well [82]. Thus, depletion of Pin1 could accelerate neuronal cell death in AD patients. Since stabilization of the p65/Rel subunit of NF- κ B by Pin1 no longer takes place, it will ultimately lead to a downregulation of anti-apoptotic genes and, ultimately, to cellular death.

MECHANISMS RELATING TYPE-2 DIABETES MELLITUS AND ALZHEIMER'S DISEASE

Since the Rotterdam study and other studies linked DM with an increased risk to develop AD, researchers worldwide have searched for the causal mechanisms

underlying this relationship. Because the NF- κ B pathway plays a major role in the etiology of both diseases, it seems reasonable to assume that mechanisms causing disturbances in this pathway are at the core of the relationship (Fig. 3). A number of issues relevant to this possibility need to be addressed.

First, in addition to their role in inflammation and immune responses, neurons and their neighboring glial cells also employ the NF- κ B pathway for distinctive functions ranging from the development to the coordination of cellular responses to injury of the nervous system, and to brain-specific processes such as the synaptic signaling that underlies learning and memory. Interestingly, electrical activity within neurons and synaptic transmission between neurons are potent stimuli for NF- κ B activation, and such neuronal activity may account for the relatively high constitutive activity of NF- κ B in brain tissue compared with other tissues [28]. As in other organs, NF- κ B influences the expression of a complex array of genes in the nervous system, and, in general, these genes serve important functions in cellular responses to injury and in neuronal plasticity. In the nervous system, the cell type and the duration of NF- κ B activation appears to be a determining factor for the output of NF- κ B in neurodegenerative diseases such as AD. NF- κ B activation in neurons has been shown to promote the survival and plasticity of these neurons. On the other hand, NF- κ B activation in glial cells may play a major role in inflammatory processes that can damage and kill neurons. Indeed, in some cases, the NF- κ B and the NF- κ B responsive genes may serve dual functions. In neuronal cells, sustained activation of NF- κ B has been shown to induce neuroprotection via PI3-kinase-PKB/Akt pathway activation [20]. Furthermore, NF- κ B cellular survival functions underlie cytokine-induced neuroprotective mechanisms, including transforming growth factor- β 1 (TGF- β 1) and TNF- α . Although transient activation of NF- κ B in activated glial cells is beneficial for defense processes, either chronic activation or overactivation may exacerbate neuronal diseases as seen in AD [83].

The second issue relates to the use of substrates for metabolic purposes. Although the brain preferentially utilizes glucose as the main substrate, ketone bodies may replace glucose as the major energy source. The liver is the main source for elevated ketones in the circulation (e.g., in starvation or hypoglycemia), but glial cells are also suitable to engage in ketone body production via stimulation of AMP-activated protein kinase (AMPK), a highly conserved stress-activated kinase [84,85]. Sustained glucoprivation and hypox-

ia, however, may cause neurons to release glutamate, which in turn leads to chronic activation of the NF- κ B pathway in glia cells and their pro-inflammatory actions.

The third issue relates to the fact that glial cells require insulin for glucose uptake (i.e., which is comparable to peripheral tissue), whereas neuronal glucose uptake is independent of insulin [86]. Thus, in the case of insulin resistance, which underlies T2DM, this would result in a limitation of glucose uptake in glial cells but not in neurons. In fact, in the case of T2DM, neurons often evidence elevated levels of glucose, which may cause direct deleterious effects via the RAGE pathway [87]. A reduction in glucose availability at the level of glial cells might be expected to cause augmented ketone body production and the chronic activation of the NF- κ B pathway with the resulting inflammatory assaults on neuronal tissue, a scenario which is somewhat comparable to the recent discussion by Erol [88]. Here, we suggest a more central role for the NF- κ B pathway than has been put forward previously. Whether this scenario can explain the causality, however, is still under investigation. Moroz and colleagues recently found that mice chronically subjected to a high-fat diet displayed all the characteristics of peripheral and central insulin resistance, but signs of AD were only marginally observed [89]. Future experiments must address species differences (e.g., the variation of cholesterol metabolism in mice and in humans [90]), timing and lifespan or aging [91], and environmental challenges (e.g., psychological stress), of all which could act as additional factors interacting in the causal link between T2DM and AD. One particularly interesting permissive mechanism linking insulin and A β , which plays a central role in development of both diseases, is the insulin-degrading enzyme (IDE). In addition to defining a key role for IDE in both A β and insulin metabolism *in vivo*, selective deletion of the IDE gene recapitulates some of the hallmark phenotypic characteristics of AD and T2DM, namely chronic elevation of cerebral A β , as in AD, and hyperinsulinemia and glucose intolerance, as in T2DM [92]. The state of chronic inflammation has great influence on the metabolism of A β and insulin. For example, in AD chronic inflammation and augmented NF- κ B, activation leads eventually to elevated A β levels, activation of glia cells, and increased cytokine release. Furthermore, pro-inflammatory cytokines can directly reduce the expression of IDE [93], which would compromise the clearance of A β and promote its aggregation. In T2DM, elevated levels of pro-inflammatory cytokines

such as TNF- α are known to induce insulin resistance in peripheral tissues by reducing insulin receptor substrate (IRS-1) phosphorylation [94] (Fig. 3).

Perez and colleagues [95] reported that the IDE activity may be reduced in AD patients compared to controls. IDE levels are reduced in diabetic A β PP transgenic mice that have increased cerebral A β levels compared to non-diabetic A β PP transgenic controls [96]. Clinical studies show that IDE levels are decreased in the hippocampi of AD patients who have the apolipoprotein ϵ 4 gene [97]. In this context, it is interesting to note that hippocampal volume is reduced in AD patients several years before any symptoms can be detected [98].

A recent paper showed that impaired insulin signaling can also lead to tau hyperphosphorylation in an animal model for DM [99]. Insulin and insulin-like growth factor-1 stimulation reduces tau phosphorylation and promotes tau binding to microtubules. These effects of insulin and insulin-like growth factor-1 are mediated through inhibition of glycogen-synthase kinase-3 via the phosphatidylinositol 3-kinase/protein kinase B signaling pathway [100]. It is known that insulin and the A β protein compete for binding to the insulin receptor [101]. A β co-immunoprecipitates with the insulin receptor and interferes with the autophosphorylation of the insulin receptor induced by insulin that affects downstream targets such as Erk/MAPK, CaMKII and PKB/Akt [102,103]. Insulin resistance or hypoinsulinemia cause elevated glucose levels which in turn leads to increases in AGEs. As the RAGE activates NF- κ B, it is conceivable that such an inflammatory precondition might increase the risk for the onset of AD.

All of these mechanisms reflect the variety of links between T2DM and AD and how this linkage might lead to pre-conditions favoring the development of AD. However, it is also conceivable that central signal mechanisms preceding the phase of clinical symptoms of AD might also aggravate or favor T2DM.

CONCLUSIONS AND FUTURE PERSPECTIVES

It is clear from the reviewed literature that inflammatory processes are playing essential roles in the etiology of T2DM and AD. Aberrant regulation of the inflammatory pathway involving NF- κ B, which includes TNF- α dependent (canonical) and TNF- α independent (non-canonical) mechanisms, directly underlies insulin resistance in peripheral tissue as well as in astrocytes

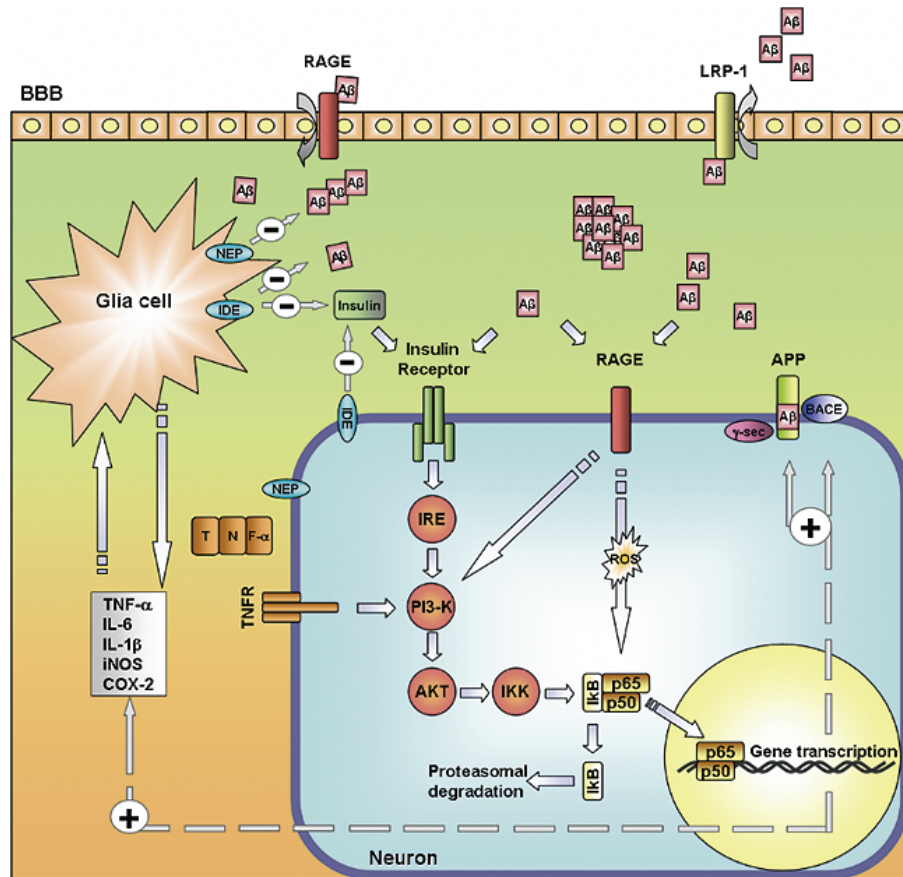


Fig. 3. Schematic representation of molecular pathways linking the pathogenesis of T2DM and AD. Conditions such as oxidative stress, pro-inflammatory cytokines, activated RAGE, and insulin receptor stimulation can directly or indirectly, lead to sustained activation of NF- κ B (p50/p65). Upon phosphorylation, I κ B becomes degraded and NF- κ B can translocate into the nucleus to initiate NF- κ B dependent gene transcription (e.g., TNF- α , IL-6, IL-1 β , iNOS, COX-2, BACE, A β PP). A β monomers and oligomers activate RAGE, whereas insulin and the A β protein compete for binding to the insulin receptor. Pro-inflammatory cytokines can directly reduce the expression of IDE, which would compromise the clearance of A β and insulin in the extracellular domain. A β , amyloid- β peptide; A β PP, amyloid- β protein precursor; AKT, protein kinase B/AKT; BACE, β -secretase; γ -sec, γ -secretase; IDE, insulin degrading enzyme; IKK, inhibitor of κ B kinase; I κ B, inhibitor of κ B; IRE, insulin response element; LRP-1, Low density lipoprotein-related protein 1; NEP, neprilysin; PI3-K, phosphoinositide-3 kinase; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α ; TNF-R, TNF receptor; Dashed arrow: indirect effect; Full arrow: direct effect. +, positive stimulation; -, inhibitory effect.

in the brain. Since insulin resistance in the periphery can lead to glucose intolerance, neuronal inflammatory processes triggering (or triggered by) the NF- κ B pathway may be propagated even further via stimulation of the AGE/RAGE signaling pathway. Therefore, it might be expected that alleviating symptoms of T2DM may be an effective way to treat AD. Indeed, recent clinical trials with the insulin sensitizer rosiglitazone, i.e., an agonist for the peroxisome proliferator-activated receptor γ (PPAR γ), whose biological actions are to regulate glucose and lipid metabolism and suppress inflammatory gene expression, have shown a significant improvement in memory and cognition in AD patients [104]. The currently used multi-target-

directed ligand (MTDLs), usually including a mix of inhibitors of acetylcholinesterase (AChE) and of monoamine oxidase (MAO) [105] may be complemented with ligands (NSAIDs, PPAR γ agonists) that improve metabolic functions of neurons and microglia, in order to delay or prevent deterioration of AD.

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